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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,186	06/02/2005	Niall Gormley	2713-1-016PCT/US	1271

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EXAMINER	
SHAW, AMANDA MARIE	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,186	GORMLEY, NIALL	
	Examiner	Art Unit	
	Amanda M. Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,10,11 and 19-32* is/are pending in the application.

4a) Of the above claim(s) *29-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,10,11 and 19-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/30/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed March 30, 2007. Applicant's arguments have been fully considered. All rejections not reiterated herein are hereby withdrawn. This action is made FINAL.

Claims 1-2, 10-11, 19-32 are currently pending. Claims 1-2, 10-11, and 19-26 have been amended. Claims 27-32 are newly presented.

Newly submitted claims 29-32 are directed to an invention that is independent or distinct from the invention originally claimed. Related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the invention originally claimed has different process steps and different objectives from the newly claimed invention. The method of the originally claimed invention is drawn to detecting a methylated cytosine in template nucleic acid. The method requires providing either a hairpin template complex or an anchor complex, each having a 5' overhang, sequencing the 5' overhang and detecting a methylated cytosine. The method of the newly claimed invention is drawn to a method for detecting methylated cytosine in a pool of template nucleic acids. The methods requires additional steps that are not performed in the originally claimed invention such as splitting a pool of template nucleic acid into two portions and treating one of the portions with bisulfite. Furthermore, the inventions as

claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants. Thus the newly claimed invention is considered a distinct invention.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 29-32 have been withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Therefore Claims 1-2, 10-11, and 19-28 will be addressed herein.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

THE FOLLOWING IS A NEW.GROUND OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS: Specifically the new rejections were required because the Applicants added the limitation "having a covalently attached 5' overhang" to claims 1, 10, 19, 21, 23, and 25.

4. Claims 1 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lackey et al (US Patent 5652126 Issued 1997) in view of Cheeseman et al (US Patent

5302509 Issued 1994) and in further view of Ulmer et al (US Patent 5674743 Issued 1997).

Lackey et al teach a hairpin template complex having a covalently attached 5' overhang (See Fig 4) and an anchor template complex having a covalently attached 5' overhang (See Fig 6). Lackey further teaches that 3'-OH terminus serves as the initiation site for synthesis via sequential addition of dNTPs in the 5' to 3' direction (Column 11). Lackey also teaches that the primer extension product can have at least one cleavage site which allows for the removal of the primer extension product so that that the hairpin template complex can be reused (Columns 12-13).

Lackey et al do not teach a method wherein the sequence of the nucleic acid template is determined as dNTPs are added to the 3' end of the hairpin which acts as a primer.

However Cheeseman teach a method for determining the sequence of nucleotides on a template strand of DNA. Specifically Cheeseman teach a single stranded DNA (which acts as a template) hybridized to an oligonucleotide primer. Fluorescently labeled 3'-blocked nucleotide triphosphates, with each of the bases A, G, C, T having a different fluorescent label, are mixed with the bound DNA molecule in the presence of DNA polymerase. The DNA polymerase causes selective addition of only the complementary labeled NTP, thus identifying the next unpaired base in the unknown DNA strand. The 3'-blocking group is then removed, setting the system up for the next NTP addition and so on. These steps are repeated until the entire target is sequenced (Abstract). Further Cheeseman teach that there are several benefits of sequencing

while elongation is taking place. For instance Cheeseman states that (i) the rate limiting step of DNA identification is the rate of a polymerase reaction, (ii) the method is more sensitive therefore smaller quantities of DNA are needed, and (iii) the reagents required for sequencing only require a single mixture of bases rather that four separate preparations (Columns 1-2).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Lackey et al by determining the nucleic acid sequence of the template nucleic acid as dNTPs are added to the 3' end of the hairpin which acts as a primer as suggested by Cheeseman. A method of sequencing a nucleic acid in a PCR reaction while the elongation step is taking place has many advantages such as: (i) the rate limiting step of DNA identification is the rate of a polymerase reaction, (ii) the method is more sensitive therefore smaller quantities of DNA are needed, and (iii) the reagents required for sequencing only require a single mixture of bases rather that four separate preparations as taught by Cheeseman (Columns 1-2).

Further Lackey et al do not teach a method wherein after the elongated strand is nicked and strand displacement occurs (thereby recovering the original template), the template strand is then treated with sodium bisulfite and resequenced as dNTPs are added to the 3' end of the hairpin which acts as a primer. Additionally Lackey et al do not teach that by comparing the first synthesized sequence and the second synthesized sequence one can detect the presence of a methylated cytosine in the template.

However Ulmer et al teach a method wherein cytosines in sample DNA are converted to uracil by bisulfite treatment which leaves 5-methylcytosines unmodified. Comparison of the sequence of modified and unmodified DNA reveals the positions in the sequence of 5'-methylcytosine (Column 4).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Lackey and Cheeseman by sequencing a template modified with sodium bisulfite and a template unmodified with sodium bisulfite and comparing the results as suggested by Ulmer. Methods of treating nucleic acid samples with sodium bisulfite is advantageous because the treatment allows for the methylated cytosines to be distinguished from unmethylated cytosines as. Thus when the template strand is resequenced as dNTPs are added to the 3' end of the hairpin which acts a primer, the resulting strand is different from the first synthesized sequence because the template strand has been modified. Further it would be obvious to compare the first synthesized sequence and the second synthesized sequence in order to determine which cytosines are methylated.

5. THE FOLLOWING IS A NEW GROUND OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS: Specifically the new rejections were required because the Applicants added the limitation "having a covalently attached 5' overhang" to claims 1, 10, 19, 21, 23, and 25.

Claims 19, 21, 23, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lackey et al (US Patent 5652126 Issued 1997) in view of Ulmer et al

(US Patent 5674743 Issued 1997) and in further view of Cheeseman et al (US Patent 5302509 Issued 1994).

Lackey et al teach a hairpin template complex having a covalently attached 5' overhang (See Fig 4), and an anchor template complex having a covalently attached 5' overhang (See Fig 6). Lackey further teaches that 3'-OH terminus serves as the initiation site for synthesis via sequential addition of dNTPs in the 5' to 3' direction (Column 11). Lackey also teaches that the primer extension product can have at least one cleavage site which allows for the removal of the primer extension product so that that the hairpin template complex can be reused (Columns 12-13).

Lackey et al do not teach a method wherein the template nucleic acid is treated with sodium bisulfite.

However Ulmer et al teach a method wherein cytosines in sample DNA are converted to uracil by bisulfite treatment which leaves 5-methylcytosines unmodified. Comparison of the sequence of modified and unmodified DNA reveals the positions in the sequence of 5'-methylcytosine (Column 4).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Lackey et al by treating the template with sodium bisulfite as suggested by Ulmer. A method of treating a nucleic acid sample with sodium bisulfite is advantageous because the treatment allows for methylated cytosines to be distinguished from unmethylated cytosines. Thus when the template strand is resequenced as dNTPs are added to the 3' end of the hairpin which acts a primer, the resulting strand is different from the first synthesized sequence

because the template strand has been modified. Further it would be obvious to compare the first synthesized sequence and the second synthesized sequence in order to determine which cytosines are methylated.

Further Lackey et al do not teach a method wherein the sequence of the nucleic acid template is determined as dNTPs are added to the 3' end of the hairpin which acts as a primer. Additionally Lackey et al do not teach that by comparing the known template sequence with the synthesized sequence one can detect the presence of a methylated cytosine in the template.

However Cheeseman teach a method for determining the sequence of nucleotides on a template strand of DNA. Specifically Cheeseman teach a single stranded DNA (which acts as a template) hybridized to an oligonucleotide primer. Fluorescently labeled 3'-blocked nucleotide triphosphates, with each of the bases A, G, C, T having a different fluorescent label, are mixed with the bound DNA molecule in the presence of DNA polymerase. The DNA polymerase causes selective addition of only the complementary labeled NTP, thus identifying the next unpaired base in the unknown DNA strand. The 3'-blocking group is then removed, setting the system up for the next NTP addition and so on. These steps are repeated until the entire target is sequenced (Abstract). The methods of sequencing taught by Cheeseman provide many advantages such as: (i) the rate limiting step of DNA identification is the rate of a polymerase reaction, (ii) the method is more sensitive therefore smaller quantities of DNA are needed, and (iii) the reagents required for sequencing only require a single mixture of bases rather that four separate preparations (Columns 1-2).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Lackey et al by determining the nucleic acid sequence of the template nucleic acid as dNTPs are added to the 3' end of the hairpin which acts as a primer as suggested by Cheeseman. A method of sequencing a nucleic acid in a PCR reaction while the elongation step is taking place has many advantages such as: (i) the rate limiting step of DNA identification is the rate of a polymerase reaction, (ii) the method is more sensitive therefore smaller quantities of DNA are needed, and (iii) the reagents required for sequencing only require a single mixture of bases rather that four separate preparations as taught by Cheeseman (Columns 1-2).

6. THE FOLLOWING IS A NEW GROUND OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS: Specifically the new rejections were required because the Applicants added the limitation "having a covalently attached 5' overhang" to claims 1, 10, 19, 21, 23, and 25.

Claims 2, 11, 20, 22, 24, and 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lackey et al (US Patent 5652126 Issued 1997) and Ulmer et al (US Patent 5674743 Issued 1997) in view of Cheeseman et al (US Patent 5302509 Issued 1994) as applied to claims 19, 21, 23, and 25 above and in further view of Chernov et al (US 2004/0086866 Filed 10/2002).

The teachings of Lackey, Cheeseman, and Ulmer et al are presented above.

The combined references do not teach that the hairpin probes are attached to a solid substrate or that the double stranded anchors are attached to a solid support.

However Chernov et al teach that there are two main approaches to construct double stranded arrays. In the first method a single oligonucleotide strand is attached to a matrix and then duplexes were formed by hybridization of the attached strand with complementary chains. The second method is based on manufacturing dsDNA arrays by using hairpin stem loop DNA molecules (Para 0008). In both cases the arrays comprise a plurality of double stranded probes distributed over the solid support.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods of Lackey, Cheeseman, and Ulmer by using probes which are attached to a solid substrate as suggested by Chernov. Methods of using double stranded probes on microarrays were well known in the art at the time of the invention and are useful for systematic investigation of DNA protein interactions which includes investigation of recombination, transcription, replication, and also discovery and engineering of new restriction enzymes (Para 0005).

Terminal Disclaimer

7. The terminal disclaimer filed on March 30, 2007 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of any patent granted on Application 10537188 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

DIANA JOHANNSEN
PRIMARY EXAMINER